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08/087,132	07/02/93	GREGORY R	IGI012CN

CARLSON EXAMINER

18M2/1222

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ART UNIT	PAPER NUMBER
1814	34

DATE MAILED: 12/22/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6-12-95 & 8-21-95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449. (2)
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 164-201 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-163 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 164-201 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

This Office Action is in response to Papers #29 (filed June 12, 1995), and Paper #32 (filed August 21, 1995). Claims 1-163 have been cancelled. Claims 164-201 are currently pending and under examination.

Due to the cancellation of the previously examined Claims, previous rejections are withdrawn and somewhat restated below in view of the newly added Claims. Applicants arguments against the rejections are addressed.

The numbering of claims is not accordance with 37 C.F.R. § 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 C.F.R. § 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 188 and 188 have been renumbered as Claim 188 and 189, respectively.

The disclosure is objected to because of the following informalities: Often times the same acronyms are used to represent different products. Further, the name CFTR is not restrictive to activity/function of the protein. Therefore, it is suggested that the name be written out in at least the independent Claims. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 164-201 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to DNA encoding huCFTR having the sequence set forth in Table 1, the intron or intervening sequence set forth in Fig. 6, point mutations T748C with A774G and T936C alone, and low copy number plasmids. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification is non-enabling for the scope of the claimed proteins because the disclosure is not commensurate in scope with the Claims for the breadth of the various point mutations that will prevent cryptic RNA polymerase promoter activity in E. coli or that will stabilize the DNA encoding CFTR to improve E. coli viability and DNA replication/propagation. The Claims are directed to point or silent mutations placed in the DNA encoding huCFTR such that the functional CFTR is not expressed in bacterial cells. The Claims encompass point mutations within the DNA encoding CFTR wherein the point mutations are at different regions. This is particularly emphasized because the specification has only taught that a double point mutation and single point mutation have been shown to prevent CFTR expression, these mutations being in the cryptic bacterial promoter at positions 748 and 774 or 936, and the DNA encoding CFTR is over 6000 bp in length. The prevention of toxic CFTR peptide fragment expression resulting from these point mutations cannot adequately predict the successful modification of the other point mutations encompassed by the scope of these Claims because the modified positions exemplified are at different regions of this DNA and

therefore it is not evident that the various claimed point mutations would equally effect the inactivity of the cryptic RNA polymerase promoter in E. coli. This is not sufficient evidence such that one of ordinary skill in the art could reasonably place a point or silent mutation anywhere among the 6000 bases and expect that the DNA will be propagated within the bacterial host cell without expressing the E. coli toxic CFTR. Silent mutations that do not affect the transcriptional regulation of the DNA encoding CFTR would be expected not to prevent the expression of the toxic CFTR. Without guidance in the specification, it is not predictable what base mutation will prevent CFTR expression in bacteria and undue experimentation would be incurred for one of ordinary skill in the art to make all possible mutations and determine if the CFTR will be produced in functional form and be toxic to the bacterial cell.

Only the intron of Fig. 6 has been shown to enhance the growth of E. coli transfected with DNA encoding huCFTR and this intron/intervening sequence by preventing the expression of the CFTR protein. It is not predictable if a small intervening sequence or intron will sufficiently disrupt the protein synthesis and subsequent host cell death as only the 83 bp synthetic intron of Fig. 6 has been shown prevent E.coli cell death. There is no guidance as to whether endogenous introns to the huCFTR gene or any intervening sequence inserted therein are adequate to prevent CFTR expression or if there will be "read through" and additional amino acids placed between amino acids of huCFTR such that CFTR activity is not affected, for example. There is no guidance as to what comprises a "synthetic" intron such that CFTR protein synthesis is prevented as is its toxicity. Are the codons random or in a specific sequence and does it matter? It is not predictable that other sequences can lower cryptic promoter activity, or placement of the intervening sequence at positions other than 1716 and 1717 will effect cryptic promoter activity because there is no other example of such and no guidance is provided such

that one skilled in the art can reasonably expect that placement of any intervening sequence anywhere within the DNA encoding CFTR will effect cryptic promoter activity and lower CFTR toxic fragment expression and increase E. coli viability. It would require undue experimentation for one of ordinary skill in the art to determine what comprises in intron such that functional CFTR is not expressed in bacterial cells because no guidance is provided in the specification and determination of what comprises such an intron is not predictable.

The specification is further non-enabling for what is encompassed by DNAs that "includes" the disclosed sequence encoding CFTR. In fact, the specification fails to exemplify not one such "subnucleotide" within the meaning of this term. As written these Claims encompass DNAs of various lengths, DNAs that are the result of fusion gene encoding different regions of the encoded protein and so forth, as long as the amino acid composition disclosed in the sequence is contained therein. Given the scope of the various DNAs and encoded peptides within this term it is not evident that these resulting expressed peptides would be functionally active and possess the desired activity.

Low copy number vectors expressing CFTR in E. coli has been shown to improve E. coli viability. Any other alteration outside of the DNA encoding CFTR is not enabled because no guidance is provided to mutate a plasmid promoter operatively linked to the DNA encoding CFTR to reduce its expression thereof, for example. Therefore, it would require undue experimentation for one skilled in the art to alter DNA outside of the CFTR encoding region because it is not predictable how DNA other than that encoding CFTR can be altered to reduce CFTR expression and improve E. coli host viability.

Response to arguments

The Gregory Declarations A-D filed on June 12, 1995 under 37 C.F.R. § 1.131 have been considered but are ineffective to overcome the issues of enablement for all point mutations and all intervening sequencing. The DNA encoding CFTR comprises within it a *cryptic* promoter that responds to E. coli RNA polymerase such that toxic fragments of CFTR are expressed therefrom. As stated above, point mutations which effect the cryptic promoter are far-ranging at base positions 748, 774, and 936. Further, the cryptic promoter can be inactivated by an intervening sequence placed between bases 1716 and 1717. It is evident that there is not a single defined region which one can predictably mutate such that the level of CFTR toxic fragment expression will be lowered and increase E. coli viability. Concerning the intervening sequence, only the synthetic sequence has been shown to lower CFTR fragment expression, and only when placed between base positions 1716 and 1717. It is not predictable that other sequences can lower cryptic promoter activity, or placement of the intervening sequence at positions other than 1716 and 1717 will effect cryptic promoter activity because there is no other example of such and no guidance is provided such that one skilled in the art can reasonably expect that placement of any intervening sequence anywhere within the DNA encoding CFTR will effect cryptic promoter activity and lower CFTR toxic fragment expression and increase E. coli viability. Therefore, these declarations are not persuasive.

The Gregory Declarations A-D and F and the Smith Declaration E filed on June 12, 1995 under 37 C.F.R. § 1.131 are sufficient to overcome the Riordan et al. reference.

Riordan et al. is being withdrawn as prior art against the now claimed invention. Riordan et al. teach DNA encoding CFTR in Fig. 2 and anticipates DNA encoding CFTR in and of itself. However, this DNA is comprised of overlapping cloning segments and is not a continuous DNA sequence ready for placement into a plasmid and to transform a host cell. Though it is obvious to get the full-length DNA encoding CFTR for cell transformation and expression using art-recognized techniques, one would have to additionally know that the expression of the full-length DNA encoding CFTR would destroy the E. coli expressing the CFTR in order to prevent the CFTR expression in E. coli by stabilizing the DNA encoding CFTR as set forth in the Claims. The placement of specific point mutations or intervening sequences to stabilize the DNA encoding CFTR to prevent toxic levels of expression in E. coli is not predictable for the reasons set forth above and are therefore not obvious.

The Examiner will not address Office Actions in other applications. The instant application is the application under examination.

The Examiner believes that all pertinent arguments have been addressed.

Note to Applicants

Allowable subject matter has been indicated since Paper #12 (mailed 11-23-93) and the Examiner has also drafted allowable claims for Applicants (fax, 11-7-94). Applicants are urged to amend their Claims accordingly.

Serial Number 08/087132

Art Unit 1812

No Claims are allowed.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D., whose telephone number is (703) 308-0034. The Examiner can normally be reached Monday through Thursday from 7:00 A.M. to 4:30 P.M. The Examiner can also be reached on alternate Fridays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Robert A. Wax, can be reached at (703) 308-4216. The fax phone number for Group 1800, AU 1814, is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

pcc
12-13-95

ROBERT A. WAX
SUPERVISORY PATENT EXAMINER
GROUP 180